

Antidiabetic, Antihyperlipidaemic and Antioxidant Activity of *Oxalis corniculata* in Alloxan Induced Diabetic Mice

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Abstract

The present study has been designed to evaluate the antidiabetic, antihyperlipidemic and antioxidative effect of *oxalis corniculata* in alloxan induced diabetic mice. Diabetes was induced in swiss albino mice by administration of alloxan monohydrate (120mg/kg body weight, ip). The aqueous extract of *oxalis corniculata* at a dose 100mg/kg body weight was administered orally at a single dose per day to diabetes induced mice for a period of ten days. The effect of aqueous extract of *oxalis corniculata* on various biochemical parameters such as blood glucose, lipid profile, liver marker enzymes, lipid peroxidation, enzymic and non enzymic antioxidants were analysed. All these effects were compared with glibenclamide as a reference antidiabetic drug. Oral administration of aqueous extract of *oxalis corniculata* for ten days elicited significant reduction in blood glucose level, lipid parameters except HDL-c, serum enzymes and significant increase in the level of HDL-C, enzymic and non enzymic antioxidants. Treatment with aqueous extract of *oxalis corniculata* also reduced the TBARS levels. From the results, the aqueous extract of *oxalis corniculata* proves to scavenge free radical and found to possess antidiabetic, antihyperlipidemic and antioxidant property against alloxan induced diabetes mellitus.

Key words: Antidiabetic, Antihyperlipidaemic, *oxalis corniculata*, antioxidants.

1. Introduction

Diabetes is a heterogeneous metabolic disorder characterized by altered carbohydrate, lipid, and protein metabolism which causes hyperglycemia resulting from insufficient insulin secretion, insulin action or both (Joseph and Jini 2011). Globally, diabetes mellitus presents enormous and increasingly important public health issues. Consequently, Diabetes places a severe economic burden on governments and individuals. There is currently fast-growing diabetes pandemic (Frances *et al.* 2012). It was estimated 285 million people worldwide with diabetes in 2010, the global burden of diabetes is expected to reach 439 million by the year 2030 (Journal of Diabetes 2012).

Dietary restrictions, exercise and administration of oral glucose lowering agents are applied widely to control blood glucose concentrations as tightly as possible (Shieh *et al.* 2011). Moreover, herbal supplements and other alternative medicines have gradually increased to be used for treatment of diabetic disorders (Chengwu Song *et al.* 2011). Extensive research has focused on exploring the hypoglycaemic activity and the active compounds of various herbal plants.

Oxalis corniculata L., Oxalidaceae, a subtropical plant being native of India, are commonly known as creeping wood sorrel. It is a delicate-appearing, low growing, herbaceous plant and abundantly distributed in damp shady places, roadsides, plantations, lawns, nearly all regions throughout the warmer parts of India, especially in the Himalayas up to 8,000 ft- cosmopolitan (Kirtikar and Basu 1975a). Traditionally the plant is well known with its versatile medicinal uses likely treatment for relieve the intoxication produced by *Datura*, as a refrigerant (Mohammad and Mir 2000a), decoction of roots is useful for worms, giddiness, diarrhoea and dysentery (Kirtikar and Basu, 1975b). The leaves are useful for cough, cold, fever and as antihelmintic. The leaves are useful for stomach ache, stop bleeding from wounds and as antihelmintic (Mohammad and Mir 2000b). Recently its anticancer activity was established which produced amazing out come from the study (Kathiriya *et al.* 2010). Phytochemical investigations of *O. corniculata* have revealed the presence of tannins, palmitic acid, a mixture of oleic, linoleic, linolenic and stearic acids (Raghvendra *et al.* 2006). Methanolic and ethanolic extracts of this plant show the presence of carbohydrate, glycosides, phytosterols, phenolic compounds, flavanoids, proteins (12.5%), amino acids and volatile oil. It also showed the presence of calcium, fiber and tannin. Leaves contain tartaric acid and citric acids, calcium oxalate, flavones etc (Unni *et al.* 2009). Considering the therapeutic potential of *oxalis corniculata*, the aim of the present investigation is to study and evaluate the antidiabetic, antihyperlipidaemic and antioxidative effect of the plant aqueous extract on alloxan induced diabetic mice.

2. Materials and Methods

2.1 Collection of plant sample

The plant *oxalis corniculata* was freshly collected from Avinashilingam University for Women, Coimbatore, Tamil Nadu, India. The plant was identified and authenticated by Dr. G.V.S. Murthy scientist 'F' and Head of office, Botanical survey of India, Tamil Nadu Agricultural University Coimbatore. A voucher specimen

(No 1736) was deposited in the Department of Biochemistry, Avinashilingam University For Women, Coimbatore, Tamilnadu, India.

2.2 Preparation of Plant Extract

The collected plant parts (whole herb) were separated from undesirable materials or plant parts. The Whole plant of *oxalis corniculata* was washed and air dried in the shade at room temperature for seven days. The dried sample was powdered and 5g of powdered plant sample was extracted with 100ml aqueous by the method of continuous hot extraction (70° C) for 6 hours. The aqueous extract solution was distilled and air dried in vacuum. The obtained residue was stored in airtight container in refrigerator below 10°C for further studies.

2.3 Induction of diabetes

Diabetes was induced in the experimental animals by a single intra peritoneal injection of Alloxan monohydrate (120mg/kg body weight) in a freshly prepared saline (0.9%) in a volume of 1ml/kg body weight after an overnight fast. Alloxan injected animals were given 20% glucose solution for 24hrs to prevent initial drug induced hypoglycemic mortality. Diabetes was confirmed by measuring fasting blood glucose concentration. After 96 hours of alloxan administration, mice with moderate diabetes having hyperglycemia (i.e. with blood glucose of 200-300 mg/dl) were taken for the experiment.

2.4 Experimental Design

The animals were divided into five groups comprising six animals in each group. All treatments were given orally to experimental animals. The experimental animals were treated ten days as follows:

GROUP I: Normal control mice, given only normal saline

GROUP II: Diabetic control mice (120 mg/kg body weight).

GROUP III: Diabetic mice given standard drug glibenclamide (570µg/kg body weight).

GROUP IV: Diabetic mice given aqueous extract of *oxalis corniculata* (100 mg/kg body weight)

GROUP V: Control mice given aqueous extract of *oxalis corniculata* (100 mg/kg body weight)

2.4.1 Biochemical assays

After ten days of treatment, the animals were deprived of food overnight and were anaesthetized using chloroform. Blood was collected in tubes with ethylene diamine tetra acetic acid (EDTA) for the estimation of blood glucose. Liver was immediately dissected out, washed in ice cold phosphate buffered saline, patted dry, weighed and analyzed for various antioxidant assays and Histopathological studies. For estimating lipid profile, serum was separated from the blood. Blood glucose was estimated by O- toluidine method. Glucose levels were expressed as mg/dl. Serum total cholesterol (TC), triglycerides (TG) and HDL cholesterol were estimated by using respective diagnostic kits. LDL and LDL cholesterol were calculated as per Friedewald's equation.

$$\text{VLDL cholesterol} = \frac{\text{Serum triglyceride} - \text{Cholesterol}}{5}$$

LDL- Cholesterol = Serum total cholesterol - VLDL cholesterol - HDL cholesterol.

Serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) was measured spectrophotometrically by utilizing the method of Reitman and Frankel (1934). Serum alkaline phosphatase (ALP) was measured by King and Armstrong (1934). Catalase (CAT) was measured by the method of Luck (1974). Superoxide dismutase (SOD) was measured by Misra et al. (1972). The level of lipid peroxidation was estimated spectrophotometrically by thiobarbituric acid reactive substances (TBARS) method, as described by Ohkha et al. (1979). Reduced glutathione (GSH) was estimated by Moran et al. (1979). Glutathione peroxidase (G-PX) was measured by the method of Pagila and Valentine (1967). Vitamin C was determined by Roe and Kuether (1953) and alpha tocopherol was analyzed by Rosenberg (1992).

2.4.2 Effect of aqueous extract of *oxalis corniculata* on histopathology of liver

At the end of the treatment period, the liver tissue of different experimental animals was removed and histological studies were carried out to reveal the aqueous extract of *oxalis corniculata*. Histopathological analysis is done by the usual method of paraffin embedding. Sections of 1-3µm thickness were histochemically react with haematoxylin and eosin staining and were evaluated for pathological changes using binocular light microscope.

2.5 Statistical Analysis

The results are expressed as the mean ± SD. The data from biochemical determinations were analyzed using Student's t-test.

3. Results

3.1 Effect of aqueous extract of *oxalis corniculata* on blood sugar level

Fig 2 shows that in normal control group (group I) treatment with normal saline alone did not affect the normal blood glucose concentration. Alloxan treatment resulted in a significant increase in blood glucose level in group II animals from 112.5±9.574 to 322.5±21.016mg/dl. These values were considerably higher than that of group I, in which normal blood glucose concentration 112.5±9.574. Oral administration of aqueous extract of *Oxalis corniculata* at a dose of 100 mg/kg body weight showed significant decrease in blood glucose in group IV after

ten days treatment indicated antidiabetic potentials of the extract.

3.2 Effect of aqueous extract of *oxalis corniculata* on lipid profile

Table 3 show the results of the antihyperlipidemic effect of *Oxalis corniculata*. The serum TC, TG, LDL, and VLDL cholesterol levels elevated significantly in diabetic control (group II) as compared to normal control group (group I), whereas HDL cholesterol reduced significantly in untreated diabetic control group (group II). All serum lipid profile parameters improved towards their near normal values after ten days treatment with aqueous extract of *oxalis corniculata*.

3.3. Effect of aqueous extract of *oxalis corniculata* on liver marker enzymes

The effects of aqueous extract of *oxalis corniculata* and glibenclamide on liver marker enzymes were shown in table 4. The diabetic mice (Group II) had increased levels of liver marker enzymes such as SGPT, SGOT, and ALP when compared with normal control. In the present study there was a significant decrease in the level of SGOT, SGPT and ALP after treatment with aqueous extract of *oxalis corniculata* and glibenclamide.

3.4. Effect of aqueous extract of *oxalis corniculata* on enzymic antioxidants of liver

The activities of SOD, CAT and GPx in the alloxan induced diabetic mice were illustrated in table 1. In the present study, the alloxan induced diabetic mice had showed significant decrease in the activities of enzymic antioxidants (SOD, CAT and G-Px). Treatment with aqueous extract of *oxalis corniculata* and glibenclamide showed reversal of all these parameters to near normal levels.

3.5 Effect of aqueous extract of *oxalis corniculata* on non enzymic antioxidants of liver

The levels of α tocopherol, ascorbic acid and reduced glutathione in the alloxan induced diabetic mice were given in table. In the present study, the levels of α tocopherol, ascorbic acid and reduced glutathione were found to be significantly decreased in alloxan diabetic mice. Treatment with aqueous extract of *oxalis corniculata* and glibenclamide showed significant increase in the level of α tocopherol, ascorbic acid, and reduced glutathione. (Table 2)

3.6. Effect of aqueous extract of *oxalis corniculata* on lipid peroxidation

The level of LPO significantly increased in alloxan induced diabetic mice when compared with normal mice. Whereas animals treated with glibenclamide and aqueous extract of *oxalis corniculata* showed significant decrease in the level of lipid peroxidation in liver. In the present study the level of lipid peroxidation was also found to be significantly decreased in aqueous extract of *oxalis corniculata* treated alloxan induced diabetic mice than the glibenclamide treated diabetic mice. (Fig 3)

3.7 Effect of aqueous extract of *oxalis corniculata* on histopathology of liver

Histopathological examination of liver of control mice showed that the central veins, the portal tracts, sinusoids and kuppfer cells appear normal. In the liver of diabetic control mice there was a focal micro vesicular and macro vesicular steatosis and also patchy periportal chronic inflammatory cell infiltration is noted. In glibenclamide treated mice the hepatocytes were normal similar to that of control. In diabetic mice treated with aqueous extract of *oxalis corniculata*, the hepatocytes are normal. In *oxalis corniculata* treated mice the central veins, portal tracts, sinusoids and kuppfer cells appear normal. (Fig 1)

4. Discussion

Diabetes mellitus is a common disorder associated with markedly increased morbidity and mortality rate. Diabetes mellitus can be defined as a group of metabolic disease characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both resulting in impaired function in carbohydrate, lipid and protein metabolism (Zhang et al. 2006). This disease not only severely compromises the daily quality of life, but also is an unbearable burden for the public healthcare system (Jun-jie shan et al. 2009). Due to the nature and complexity of diabetes and the lack of an effective cure, traditional herbal medicine, or Alternative Medicine as it is known in the scientific world, has been explored for potential ways to control, manage and cure diabetes (Hu et al. 2003; Chau et al. 2006; Stone 2008). Common advantages of herbal medicines are effectiveness, safety, affordability and acceptability (Valiathan 1998). Medicinal plants are a rich source of natural products and their products have been widely used for treatment of diabetes all around the world with less known scientific basis of their function (Patwardhan et al. 2004; Said et al. 2007).

Oxalis corniculata Linn is an endangered and medicinally important plant indigenous to tropical and subtropical regions of the world. The present study has been designed to evaluate the antidiabetic, antihyperlipidemic and antioxidative activity of *oxalis corniculata* on alloxan induced diabetic mice. Alloxan, a beta cytotoxin, induces diabetes mellitus in mice become hyperglycemic in a short period of time, followed by hepatic glucose overproduction (Milagro et al. 2000). Intra peritoneal administration of alloxan (150mg/kg) effectively induced diabetes mellitus in normal mice (Dodamani et al. 2012). The mechanism of action is the fragmentation in pancreatic islets and cell damage has been attributed to the production of toxic free radicals (Takasu et al. 1991).

In the present study, treatment of diabetic mice with aqueous extract of *oxalis corniculata* (100mg /kg body weight) for ten days showed marked hypoglycaemic effect as compared with the diabetic non treated mice. Our results run parallel with (kala et al. 2011; Malviya et al 2010) who reported a hypoglycaemic effect of different

plant extracts. In the present investigation, glibenclamide a member of sulphonylurea used as a reference drug. It has been proposed that sulphonylurea produce their hypoglycemic effect primarily through increased release of insulin in pancreatic β cells. Thus any plant secondary metabolite or chemical constituent of which is capable of affecting the insulin secretion from pancreatic β cells will be a good mimicker of sulphonylureas (Del Prato 2006). The aqueous extract of *oxalis corniculata* found to be significantly effective in lowering blood glucose. Therefore, the extract was able to potentiate the release of insulin from pancreatic islets similar to that of results observed after glibenclamide administration.

In the present study elevated level of TG,TC,LDL and VLDL and decreased level of HDL in alloxan induced diabetic mice was observed. Treatment with aqueous extract of *oxalis corniculata* not only decreased serum TG,TC,LDL and VLDL but also increased HDL level significantly. The insulin deficiency depletes the activity level of lipoprotein lipase, thus leading to deranged lipoprotein metabolism during diabetes (Sivaraj et al. 2009). Diabetic mice treated with aqueous extract of *oxalis corniculata* and glibenclamide also normalized lipid levels. Thus the results indicate that aqueous extract also may possess insulin like action by virtue of the ability to lower the lipid levels. These results are similar to earlier reports observed with the other plant (Ragini et al. 2011).

The animals treated with alloxan developed hepatic damage which was evident from the increase in the enzyme activities. Treatment with aqueous extract of *oxalis corniculata* and glibenclamide resulted in a decrease of transaminase activities in alloxan treated animals. The serum AST and ALT levels increases as a result of metabolic changes in the liver, such as administration of toxin, cirrhosis of the liver, hepatitis and liver cancer including diabetes (Chalasanani et al. 2004). Similarly in the present study, it was observed that the levels of SGPT and SGOT in alloxan induced diabetic animals were elevated. It may be due to leaking out of enzymes from the tissues and migrating into the circulation by the adverse effect of alloxan (Stanley et al. 1999). In this study, the aqueous extract of *oxalis corniculata* regulated the activity of SGOT,SGPT and ALP in liver of animals intoxicated with alloxan. The effect of glibenclamide on the recovery of hepatic enzyme activity in serum was very similar to that of the earlier study (Hakkim et al. 2007). The results indicates that the aqueous extract of *oxalis corniculata* can reduce the level of liver marker enzymes and confirms the possibility that the major function of the extract are on the protection of liver tissues there by improves the liver function.

Diabetes may induce increased systemic oxidative stress which is underlying cause of dysregulation of adipokines and development of metabolic syndrome and pathogenesis of various diseases (Brownlee 2001). Oxidative stress impairs glucose uptake in muscle and adipose tissue in diabetic condition (Maddux et al. 2001; Rudich et al 1998) and decreases insulin secretion from pancreatic B cells (Matsuoka et al.,1997). This results to a hyperglycemic environment which may impair radical scavenging activity and hence exposing proteins and lipids to peroxidation (Gabriel et al. 2011). Our study showed a significant increase in TBARS levels in liver tissue of diabetic mice. TBARS level in liver were significantly lower in the plant extract treated group compared to the diabetic control group. These results suggests that the plant extract may exert antioxidant activities and protect the tissues from lipid peroxidation due to secondary metabolites such as alkaloids,tannins,flavanoids and cardiac glycosides present in plant (Ragavendra et al. 2006).

In recent years, plant extracts have been widely used as natural antioxidants because of the presence of polyphenolics. The presence of these phenolic and flavonoid compounds, contribute diverse biological activities such as anti-carcinogenic, anti-inflammatory, and anti-atherosclerotic. These activities might be related to their antioxidant activity (Nuengchamnong et al. 2009). The polar solvents such as methanol and water are the best solvent in extracting the flavonoid from *O. corniculata*, indicating that most of the flavonoid exists in a conjugated form through their hydroxyl groups with glycosides, lead to the increasing polarity and solubility in methanol and water (Mohsen and Ammar 2009).

In the present study, there was a significant decrease in enzymic antioxidant such as SOD, CAT and GSH non enzymic antioxidant such as vitamine E and Vitamine C in hepatic tissue of diabetic mice. These observations were accordance with the earlier reports (Raghavan 2006). Furthermore, alterations in the antioxidant parameter during diabetes induced oxidative stress have also been reported. The phenolic and flavanoid content in the plant extract may be responsible for its free radical scavenging activity. These adverse changes were reversed to near normal values in aqueous extract of *oxalis corniculata* mice as well as glibenclamide treated mice. Thus, the inhibitory effects of the plant extract on oxidative damage may be attributed to the suppression induced peroxidation (selvendran et al. 2004).

In our studies damage of liver tissue was observed in alloxan induced diabetic control mice. The reference drug glibenclamide treated group showed regeneration of β cells. The comparable regeneration was also shown by aqueous extract of *oxalis corniculata*. Photomicrographs reinforce healing of liver by the aqueous extract of *oxalis corniculata* as a plausible mechanism of their antidiabetic activity.

In conclusion, there is enough evidence to support that the aqueous extract of *oxalis corniculata* exhibited antidiabetic activity, strong antioxidant activity and free radical scavenging activity. The antidiabetic, antihyperlipaemic and antioxidant activity of aqueous extract of *oxalis corniculata* as observed in our study is due to its stimulatory effect on both enzymatic and non enzymatic antioxidant system in the

experimental mice. The result obtained from this study has provided scientific credence to the ethonotherapeutic usage of this plant traditionally.

Further studies are needed to elaborate whether some other compounds present in *oxalis corniculata* are also responsible for the protective effect against diabetes mellitus and oxidative damage and the molecular basis of their mode of action.

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Table.1. Effect of aqueous extract of *Oxalis corniculata* on Enzymatic Antioxidants in the liver of control and experimental animals

| Treatment Groups | Enzymatic Antioxidants(Units/mg) | | |
|--|----------------------------------|-------------|-------------|
| | CAT | SOD | G-PX |
| Gr. I:Normal Control | 34.00±5.943 | 3.433±1.850 | 5.900±1.277 |
| Gr.II:Diabetic control(120 mg/kg) | 14.10±6.702 | 2.400±0.100 | 2.33±0.945 |
| Gr.III:Alloxan+Glibenclamide(570µg/kg) | 42.26±6.099 | 4.000±0.794 | 5.933±0.814 |
| Gr.IV :Alloxan +Aqueous plant extract (100mg/kg) | 55.43±6.369 | 6.600±1.082 | 8.237±1.438 |
| Gr.V :Aqueous extract alone(100 mg/kg) | 63.00±1.473 | 7.337±0.283 | 9.107±0.280 |

The values are mean±SD of six animals in each group

Table.2. Effect of aqueous extract of *Oxalis corniculata* on non enzymatic Antioxidants in the liver of control and experimental animals

| Treatment Groups | Non EnzymaticAntioxidants(Units/Mg) | | |
|--|-------------------------------------|--------------|-------------------|
| | Vit C(µg/g) | vit E(mg/g) | Glutathione(µg/g) |
| Gr. I:Normal control | 22.750±1.439 | 0.0210±0.001 | 0.111±0.009 |
| Gr.II:Diabetic control(120 mg/kg) | 11.653±0.562 | 0.0178±0.000 | 0.0116±0.000 |
| Gr.III:Alloxan+Glibenclamide(570µg/kg) | 33.667±1.528 | 0.0220±0.001 | 0.167±0.020 |
| Gr.IV :Alloxan +Aqueous plant extract (100mg/kg) | 34.167±0.764 | 0.0246±0.022 | 0.121±0.007 |
| Gr.V :Aqueous extract alone(100 mg/kg) | 37.000±2.000 | 0.0237±0.001 | 0.135±0.035 |

The values are mean±SD of six animals in each group

Table.3. Effect of aqueous extract of *oxalis corniculata* on lipid profile of control and experimental animals

| Treatment groups | TC | HDL | TG | LDL | VLDL |
|------------------|--------------|--------------|---------------|--------------|------------|
| Gr.I | 148.38±0.110 | 34.75±0.250 | 112.317±0.165 | 91.50±0.707 | 23.5±2.121 |
| Gr.II | 212.90±0.300 | 24.13±0.0153 | 161.202±1.982 | 155.00±1.414 | 33.0±1.414 |
| Gr.III | 154.80±0.608 | 34.32±0.140 | 128.5±4.950 | 93.5±2.121 | 26.5±2.121 |
| Gr.IV | 93.54±0.153 | 29.63±0.275 | 121.5±2.121 | 90.5±0.707 | 25.5±2.121 |
| Gr.V | 103.22±0.354 | 41.37±0.0651 | 111.5±0.707 | 89.75±1.061 | 23.0±1.414 |

The values are mean±SD of six animals in each group

Table. 4. Effect of aqueous extract of *oxalis corniculata* on liver marker enzymes of control and experimental animals

| Treatment Groups | Liver Marker Enzymes (IU/L) | | |
|--|-----------------------------|-------------|------------|
| | SGOT (IU/L) | SGPT(IU/L) | ALP(IU/L) |
| Gr.I:Normal control | 21.0±0.707 | 35.25±0.354 | 1.3±0.141 |
| Gr.II:Diabetic Control(120mg/kg) | 56.55±0.106 | 104.5±0.707 | 3.5±0.141 |
| Gr.III:Alloxan+ Glibenclamide (570µg/kg) | 27±1.414 | 37±1.414 | 2.3±0.141 |
| GrIV: Alloxan+extract(100mg/kg) | 26.5±0.707 | 30.55±0.070 | 2.25±0.070 |
| GrV:Extract alone (100mg/kg) | 20.5±0.707 | 37.5±2.121 | 1.45±0.778 |

The values are mean±SD of six animals in each group

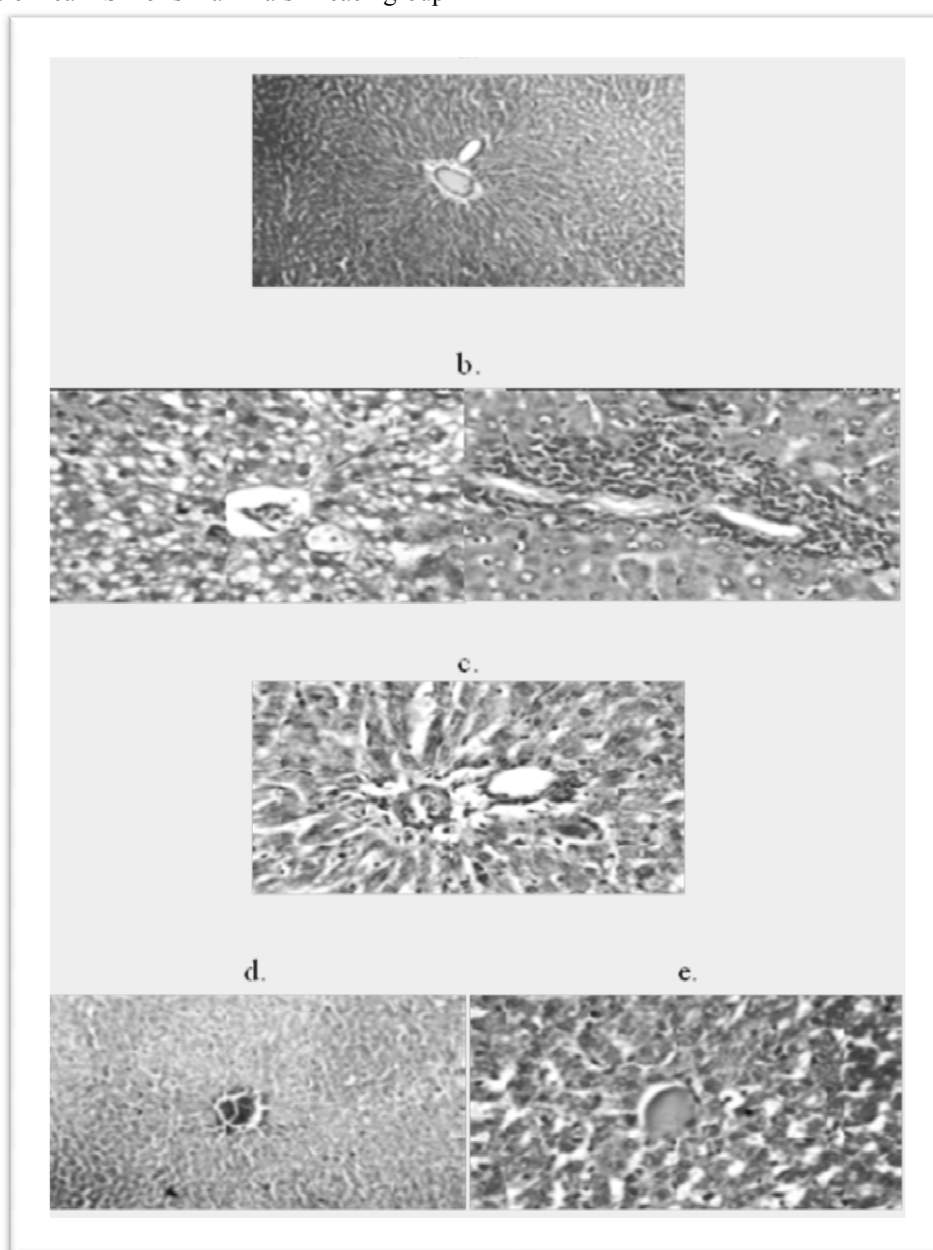


Figure .1. Photomicrograph showing histological sections of liver of mice of different groups. (a)Group I liver, (b) Group II liver, (c) Group III liver, (d) Group IV liver (e) Group V liver

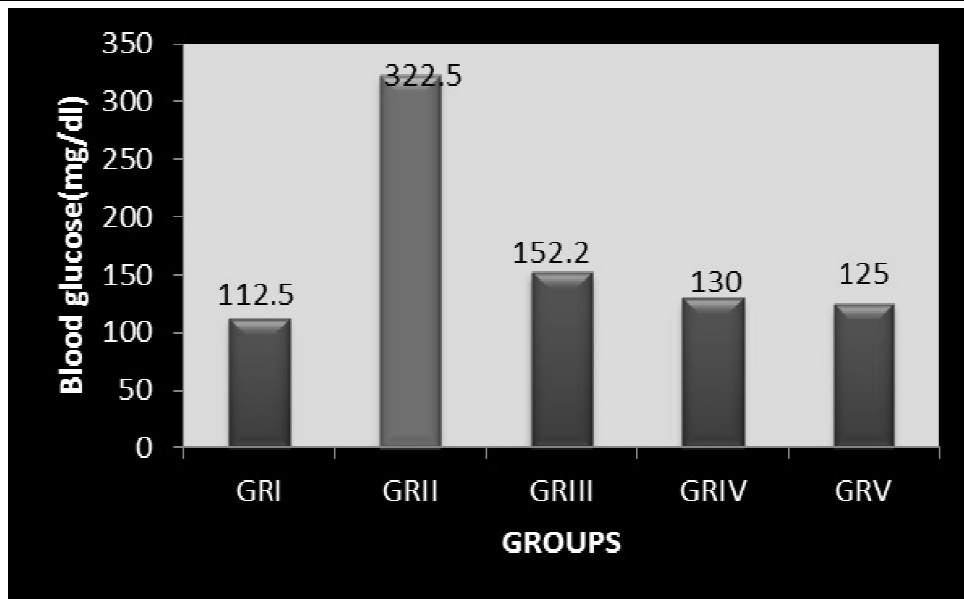


Figure .2. Effect of aqueous extract of *oxalis corniculata* on blood glucose of control and experimental animals
*($P \leq 0.001$)

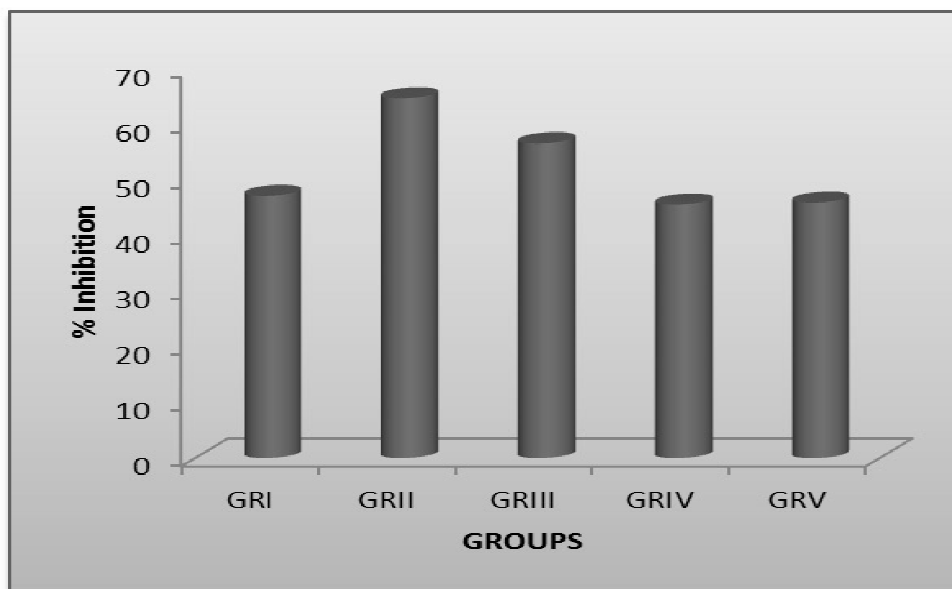


Figure.3. Effect of aqueous extract of *oxalis corniculata* on lipid peroxidation of control and experimental animals
*($P \leq 0.001$)

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